EMERGING RESEARCH FRONTS - 2008

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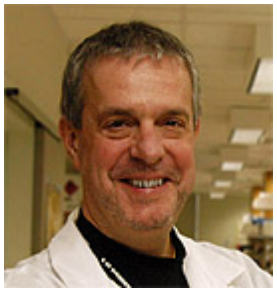
Berislav V. Zlokovic talks with *ScienceWatch.com* and answers a few questions about this month's Emerging Research Front Paper in the field of Neuroscience & Behavior.



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Article: RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain
Authors: Deane, R, et al.
Journal: NATURE MED, 9 (7): 907-913 JUL 2003
Addresses: Univ Rochester, Med Ctr, Dept Neurosurg, Frank P Smith Labs Neurosurg, Rochester, NY 14642 USA.
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(addresses have been truncated.)

SW: Why do you think your paper is highly cited?

Since the publication of our article in 2003, there has been an increased interest in RAGE (receptor for advanced glycation endproducts) as a transporter of Aß into brain, and on the effects of Aß/RAGE interaction.

Our paper showed that RAGE is increased in the blood vessels of a mouse model of Alzheimer's disease (AD), and that this increased level of RAGE is associated with greater entry of the AD toxin Aß into brain. This supports the vascular hypothesis of AD, i.e., that blood vessels contribute to the causes of AD.

This paper also showed that Aß/RAGE interaction caused the following: 1) an increased release of a chemical, endothelin-1, that causes the brain blood vessels to constrict and may contribute to reduce brain blood flow as seen in AD, 2) raised levels of oxidative stress markers, and 3) raised levels of inflammatory chemicals. Blocking the Aß/RAGE interaction prevented these responses. These studies showed that RAGE is a potential target for the development of new therapies for AD.

These studies may have stimulated research on the role of RAGE in various diseases, including AD and diabetes, and on the development of new therapies. This may have explained the high citation rate.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

Since scientific studies of this nature are published based on novelty, it's probably a new discovery.

SW: Would you summarize the significance of your paper in layman's terms?

This paper shows the importance of the brain blood vessels in transporting the toxin Aß

into brain. It also identified the main transporter, RAGE, that ferries the AD toxins into brain. It also showed that Aß/RAGE interaction caused reduced brain blood flow, inflammation, and oxidative damage, which are also associated with AD. Blocking this interaction reversed these effects. RAGE is a potential target for the development of new AD therapies.

"The blood vessels of the brain are unique and form the physical site of the BBB, which restricts the passage of molecules into and out of the brain."

How did you become involved in this research and were any particular problems encountered along the way?

I was trained at the King's College London, by the renowned British physiologist, Dr. Hugh Davson—1909-1996—who was known as the father of the blood-brain barrier (BBB). A recent review on the BBB was dedicated to him (Zlokovic B, *Neuron.* 57: 178-201, 2008).

The blood vessels of the brain are unique and form the physical site of the BBB, which restricts the passage of molecules into and out of the brain. I became involved in AD research when a colleague, Dr. Blas Frangione, a Professor of Pathology and Psychiatry at the NYU School of Medicine, suggested that I applied my BBB research to AD.

We first published a study on Aß transport into the brain in 1993 (Zlokovic B, *et al*., *BBRC* 197: 1034-40, 1993). We then investigated mechanism of Aß transport into and out of the brain. Our studies showed that the main transporter that transports Aß out of the brain is LRP1 (low-density lipoprotein related protein 1), and the main transporter that transports Aß into brain is RAGE.

SW: Where do you see your research leading in the future?

My work is focused on translational research, working towards developing new therapies for AD and stroke. Regarding RAGE, we have identified a small compound that blocks the interaction of Aß with RAGE. In a mouse model of AD, this compound reduced brain Aß levels and improved functional changes in brain blood flow and behavioral performance. This compound is a potential new therapy for AD.

SW: Do you foresee any social or political implications for your research?

If this compound, or its chemical entity, became a treatment for AD and other RAGE-dependent diseases, then it may indeed have social benefits.

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Keywords: receptor for advanced glycation endproducts, aß/rage interaction, low-density lipoprotein related protein 1, reduced brain blood flow, inflammation, oxidative damage, alzheimer's disease, diabetes, endothelin-1, oxidative stress markers, inflammatory chemicals, hugh davson, blood-brain barrier.

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